FORM PTO 1390 (REV 5-93) | US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | ATTORNEY DOCKET NO. 2000_0694A

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 USC 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) NEW 09/555494

International Application No.	International Filing Date	Priority Date Claimed
PCT/JP98/05391	December 1, 1998	December 5, 1997

Title of Invention
CRYSTALLINE ANTHRACYCLINE ANTIBIOTIC AND PROCESS FOR PRODUCING THE SAME

Applicant(s) For DO/EO/US
Osamu JOHDO, Kiyotomo NAKAMURA, Takeo YOSHIOKA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 USC 371.

2. [] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 USC 371.

3. [] This is an express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 USC 371(c)(2))
   a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [X] A translation of the International Application into English (35 USC 371(c)(2)). **ATTACHMENT A**

7. [] Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3)).
   a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] have been transmitted by the International Bureau.
   c. [] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [] have not been made and will not be made.

8. [] A translation of the amendments to the claims under PCT Article 19 (35 USC 371(c)(3)).

9. [X] An **executed** oath or declaration of the inventor(s) (35 USC 371(c)(4)). **ATTACHMENT B**

10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 USC 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98. **ATTACHMENT C**
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. **ATTACHMENT D**
13. [] A FIRST preliminary amendment.
    [] A SECOND or SUBSEQUENT preliminary amendment.
14. [] A substitute specification.
15. [] A change of power of attorney and/or address letter.
16. [] Other items or information:

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEE FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975.

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) NEW 09/555494	INTERNATIONAL APPLICATION NO. PCT/JP98/05391	ATTORNEY DOCKET NO. 2000 0694A	
17. [X] The following fees are submitted		CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):			
[X] Search Report has been prepared by the EPO or JPO $840.00			
[] International preliminary examination fee paid to USPTO (37 CFR 1.482) $670.00			
[] No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $690.00			
[] Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00			
[] International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-33(4) . . . . . $ 96.00			
ENTER APPROPRIATE BASIC FEE AMOUNT =		$840.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	- 20 =		X $18.00	$	
Independent Claims	- 3 =		X $78.00	$	
Multiple dependent claim(s) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$840.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28) -				$	
SUBTOTAL =				$840.00	
Processing fee of $130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$840.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) ($40 per property). +				$40.00	
TOTAL FEES ENCLOSED =				$880.00	
				Amount to be refunded:	$
				charged:	$

a. [X] A check in the amount of $880.00 to cover the above fees is enclosed.

b. [] Please charge my Deposit Account No. 23-0975 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975. A duplicate copy of this sheet is enclosed.

***NOTE*: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

WENDEROTH, LIND & PONACK
2033 K St., N.W., Suite 800
Washington, D.C. 20006

Telephone: (202) 721-8200
Facsimile: (202) 721-8250

By Warren Cheek
Warren M. Cheek, Jr.
Registration No. 33,367

June 1, 2000
WMC/dlk

Check No. 38304

2000-0694A

DESCRIPTION

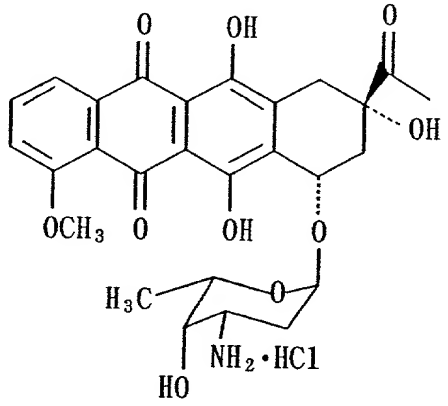
CRYSTALLINE ANTHRACYCLINE ANTIBIOTIC AND PROCESS FOR PRODUCING THE SAME

Technical Field

This invention relates to novel crystalline forms of an anthracycline antibiotic, particularly daunomycin (also known as daunorubicin), and a process for producing the same.

Background Art

Daunomycin (also known as daunorubicin; hereinafter abbreviated as DM), which is an anthracycline antibiotic represented by the following formula (I)



(I)

is known to be obtained from a culture medium of an actinomycete, and has a wide anticancer spectrum against experimental animal tumors. As a matter of fact, DM is being widely used as a chemotherapeutic agent for cancer in clinical applications.

However, the currently available bulk form of DM (DM hydrochloride) is an amorphous powder or a solid which is tentatively classified as crystalline but has high hygroscopicity and poor stability. From the viewpoint of the preparation of DM into medicines, the

physical and chemical properties of not only its final bulk powder but also its intermediate products have a great significance. For example, poor chemical stability requires great caution in storage, and high hygroscopicity makes its handling difficult. Moreover, with consideration for its use as a drug, any residual solvent may constitute a fatal shortcoming.

Accordingly, an object of the present invention is to provide a solid product of DM hydrochloride having excellent chemical stability and, preferably, further having low hygroscopicity and an allowable residual solvent content.

Disclosure of the Invention

The present inventors made repeated investigations with a view to solving the above-described problems and have now found that the crystallization of DM hydrochloride by using a certain solvent system yields a specific crystalline form of DM hydrochloride having excellent chemical stability and, in some instances, this crystalline form also has low hygroscopicity and can solve the problem with residual solvent.

Thus, according to the present invention, there is provided a crystalline form of DM hydrochloride having at least characteristic 2θ values (in degrees) of 6.18, 7.88, 9.82, 11.60, 13.30, 15.80, 20.88 and 23.12 as measured by the X-ray powder diffraction method.

According to the present invention, there is also provided a process for producing the aforesaid crystalline form of DM hydrochloride from a solution containing DM hydrochloride, the process comprising the steps of preparing the aforesaid solution by using a solvent system composed of a poor solvent for the antibiotic and a good solvent which is miscible with the poor solvent and capable of dissolving the antibiotic; and subjecting the solution so prepared to a crystallization treatment.

Brief Description of the Drawing

FIG. 1 is a chart showing the results of X-ray powder diffraction analysis of DM hydrochloride powders and various crystalline forms of DM hydrochloride. In this chart, b) shows the result of X-ray powder diffraction analysis of a crystalline form of DM hydrochloride in accordance with the present invention; a), d), e) and f) show the results of X-ray powder diffraction analysis of amorphous DM hydrochloride powders (comparative powders); and c), g) and h) show the results of X-ray powder diffraction analysis of solid forms of DM hydrochloride which are regarded as crystalline but do not show the properties of the crystalline form in accordance with the present invention (comparative crystalline forms).

Specific Description of the Invention

Specifically, the crystalline form of DM hydrochloride in accordance with the present invention are characterized by having at least characteristic 2θ values (in degrees) of 6.18, 7.88, 9.82, 11.60, 13.30, 15.80, 20.88 and 23.12 as measured by the X-ray powder diffraction method (the Debye-Scherrer method) [see b) in FIG. 1]. The term "crystalline form" as used herein means a single crystal or a mass of such crystals, and the aforesaid results of X-ray powder diffraction analysis are those obtained from such masses.

The crystalline form in accordance with the present invention are clearly distinguished from amorphous powders [corresponding to those shown as a), d), e) and f) in FIG. 1] and solid forms tentatively regarded as crystalline [corresponding to those shown as c), g) and h) in FIG. 1]. Moreover, as will be described later, the crystalline form b) have very excellent properties from the viewpoints of hygroscopicity, residual solvent and chemical stability.

Generally and not by way of limitation, the process for producing the aforesaid crystalline form in accordance with the

present invention comprises the steps of preparing a solution by dissolving a DM hydrochloride powder having a relative purity of greater than 90% in a solvent capable of dissolving the DM; and crystallizing the DM by adding to the solution a solvent which is miscible with the aforesaid solvent but is a poor solvent for DM.

It is important to use a solvent containing at least 1-butanol as the aforesaid poor solvent. Typical examples of such solvents include 1-butanol alone and solvent mixtures composed of 1-butanol and other organic solvents (e.g., acetone, hexane and diisopropyl ether). On the other hand, as the solvent capable of dissolving DM, there may be used any solvent that can dissolve DM, is miscible the aforesaid poor solvent, and hence suits the purpose of the present invention. Typical examples of such solvents include, but are not limited to, water, methanol, ethanol, and mixtures of two or more of them.

In accordance with a preferred embodiment, the production process of the present invention comprises the steps of preparing a solution by dissolving a DM hydrochloride powder having a relative purity of greater than 90% in methanol (for example, by using the DM hydrochloride powder and methanol in a weight ratio of 1 : 5 to 1 : 20); and crystallizing the DM by adding 1-butanol or a mixture of 1-butanol and acetone, hexane or diisopropyl ether (for example, containing up to 60% of acetone, hexane or diisopropyl ether) to the aforesaid solution in an amount of about 1 to 20 parts by volume as based on the methanol.

When the expression "1-butanol / acetone", for example, is used in connection with the present invention, it means the combined use of 1-butanol and acetone. Thus, according to the present invention, the solvent used to dissolve a DM hydrochloride powder may comprise not only methanol alone, but also a mixture of methanol and 1-butanol or a mixture of methanol, 1-butanol and acetone,

hexane or diisopropyl ether, provided that the mixture can dissolve the DM hydrochloride powder. Then, as a solvent for crystallization purposes, 1-butanol or a mixture of 1-butanol and acetone, hexane or diisopropyl ether is added to the DM hydrochloride solution thus obtained, so that a crystalline DM hydrochloride is formed. This crystallization step may be carried out by, after the addition of the aforesaid solvent for crystallization purposes, allowing the solution to stand at a temperature of about 5 to 35°C and preferably at room temperature (18 to 27°C), optionally with cooling (to about 5°C) and optionally with gentle stirring. The crystalline DM hydrochloride so precipitated may be collected by a per se known technique such as filtration or centrifugation.

DM hydrochloride may be obtained as a commercial product, or may be prepared according to the process described in Japanese Patent Laid-Open No. 21394/'84 (corresponding to U.S. Patent No. 4,592,999). As the starting material for use in the process of the present invention, the DM hydrochloride which has been obtained by any method may be used, provided that it suits the purpose of the present invention. However, it is generally favorable to use DM hydrochloride having a purity of not less than 90% and preferably not less than 95%.

The present invention is more specifically explained with reference to the following examples. However, it is not intended to limit the present invention to any of these examples.

Example 1 (comparative example)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of acetone was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 1.2 g of a reddish-brown powder. The result of measurement of this powder according to the X-ray powder diffrac-

tion method is shown as a) in FIG. 1. The measuring conditions included a step angle of 0.02°, a counting time of 1.0 second, a tube voltage of 40.0 kV, and a tube current of 20.0 mA (the same shall apply hereinafter).

Example 2 (the present invention)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of 1-butanol was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 1.4 g of a reddish-brown crystalline powder. The result of measurement of this powder according to the X-ray powder diffraction method is shown as b) in FIG. 1.

Example 3 (comparative example)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of ethanol was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 0.9 g of a reddish-brown crystalline powder. The result of measurement of this powder according to the X-ray powder diffraction method is shown as c) in FIG. 1.

Example 4 (comparative example)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of diethyl ether was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 1.5 g of a reddish-brown powder. The result of measurement of this powder according to the X-ray powder diffraction method is shown as d) in FIG. 1.

Example 5 (comparative example)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of 1-propanol was added to the

solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 0.9 g of a reddish-brown powder. The result of measurement of this powder according to the X-ray powder diffraction method is shown as e) in FIG. 1.

Example 6 (comparative example)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of 2-propanol was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 1.3 g of a reddish-brown powder. The result of measurement of this powder according to the X-ray powder diffraction method is shown as f) in FIG. 1.

Example 7 (comparative example)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of n-hexane was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 1.3 g of a reddish-brown crystalline powder. The result of measurement of this powder according to the X-ray powder diffraction method is shown as g) in FIG. 1.

Example 8 (comparative example)

2 g of DM hydrochloride was dissolved in 20 mL of methanol. At room temperature, 200 mL of isopropyl ether was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 1.6 g of a reddish-brown crystalline powder. The result of measurement of this powder according to the X-ray powder diffraction method is shown as h) in FIG. 1.

Example 9 (the present invention)

0.5 g of DM hydrochloride was dissolved in 5 mL of metha-

nol. At room temperature, 50 mL of a mixture (2 : 3) of 1-butanol and acetone was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 0.28 g of a reddish-brown crystalline powder. The result of measurement of this powder according to the X-ray powder diffraction method showed the same pattern as that of b) in FIG. 1.

Example 10 (the present invention)

0.5 g of DM hydrochloride was dissolved in 5 mL of methanol. At room temperature, 50 mL of a mixture (3 : 2) of 1-butanol and hexane was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 0.38 g of a reddish-brown crystalline powder. The result of measurement of this powder according to the X-ray powder diffraction method showed the same pattern as that of b) in FIG. 1.

Example 11 (the present invention)

0.5 g of DM hydrochloride was dissolved in 5 mL of methanol. At room temperature, 50 mL of a mixture (3 : 2) of 1-butanol and diisopropyl ether was added to the solution, resulting in the formation of a precipitate. This precipitate was collected by filtration and dried (under reduced pressure at 60°C for 16 hours) to obtain 0.38 g of a reddish-brown crystalline powder. The result of measurement of this powder according to the X-ray powder diffraction method showed the same pattern as that of b) in FIG. 1.

Example 12 (tests for hygroscopicity)

Samples of the powders (or crystalline powders) obtained in Examples 1-8 were stored at 30°C and at relative humidities ranging from 32 to 91%. Their moisture contents were measured until a steady state was reached. The critical relative humidities calculated from the increases or decreases in moisture content are

shown in Table 1 below.

Table 1

Powder	Ex.1	Ex.2	Ex.3	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8
Critical relative humidity (%)	34	73	41	28	29	29	41	53

It can be seen from the above-described results that the crystalline DM hydrochloride obtained in Example 2 (the present invention) has very low hygroscopicity.

Example 13 (tests for chemical stability)

Each of the same samples as used in Example 12 was placed in a hermetically sealed container and stored at 60°C for 1 month. Then, the sample was analyzed by HPLC to determine the DM content in the sample. The results thus obtained are shown in Table 2 below.

Table 2

Powder	Ex.1	Ex.2	Ex.3	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8
Amount of remaining DM (%)	91.4	100	97.1	90.4	97.5	94.2	97.2	96.5

It can be seen from the above-described results that the crystalline powder of Example 2 has excellent chemical stability.

(Conditions for analysis by HPLC)

Column: YMC A-312 (ODS) (manufactured by YMC Co., Ltd.).

Mobile phase: Acetonitrile-water (38 : 62) (adjusted to pH 2.2 with phosphoric acid).

Flow velocity: About 1.5 ml/min.

Detection: 254 nm.

Example 14 (residual solvent content)

Each of the same samples as used in Example 12 was analyzed by gas chromatography (GC) to determine its residual solvent content. The results thus obtained are shown in Table 2 below.

Table 3

Crystalline form

Powder	Ex.1	Ex.2	Ex.3	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8
Residual solvent content (%)	0.14	0.40	0.03	0.50	0.19	0.18	0.05	0.95

It can be seen from the above-described results that the residual solvent content of the crystalline powder of Example 2 is within an acceptable limit.

(Operating conditions for analysis by GC)

Detector: Flame ionization detector.

Column: Shimadzu CBP 10-S25-050.

Column temperature: Operated at 40°C for 5 minutes, and then raised to 80°C in 5 minutes and held at that temperature.

Vaporization chamber temperature: A constant temperature around 200°.

Carrier gas: Helium.

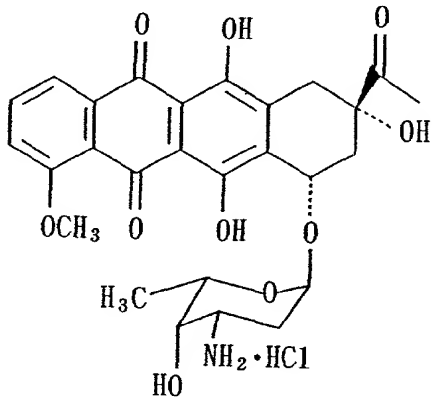
Flow rate: A constant flow rate at which the retention time of an internal standard substance (dioxane) is about 6 minutes.

Exploitability in Industry

The present invention provides crystalline forms of DM hydrochloride showing a reduction in hygroscopicity and residual solvent content and an improvement in chemical stability, as well as a process which can produce them easily. Accordingly, the present invention may be utilized, for example, in the field of the manufacture of medicines and bulk materials for medicines.

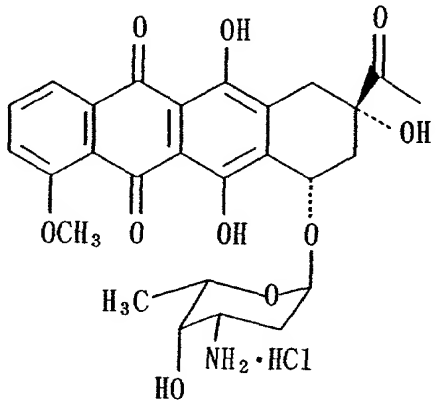
CLAIMS

1. A crystalline form of anthracycline antibiotic represented by the following formula (I) and having at least characteristic 2θ values (in degrees) of 6.18, 7.88, 9.82, 11.60, 13.30, 15.80, 20.88 and 23.12 as measured by the X-ray powder diffraction method.



(I)

2. A process for producing a crystalline form of anthracycline antibiotic represented by the following formula (I) and having at least characteristic 2θ values (in degrees) of 6.18, 7.88, 9.82, 11.60, 13.30, 15.80, 20.88 and 23.12 as measured by the X-ray powder diffraction method,



(I)

from a solution containing the antibiotic, the process comprising the steps of preparing said solution by using a solvent system composed

of a poor solvent for the antibiotic and a good solvent which is miscible with the poor solvent and capable of dissolving the antibiotic; and subjecting the solution so prepared to a crystallization treatment.

3. A process as claimed in claim 2 wherein the poor solvent contains at least 1-butanol.

4. A process as claimed in claim 2 wherein the poor solvent is selected from the group consisting of 1-butanol, 1-butanol / acetone, 1-butanol / hexane and 1-butanol / diisopropyl ether.

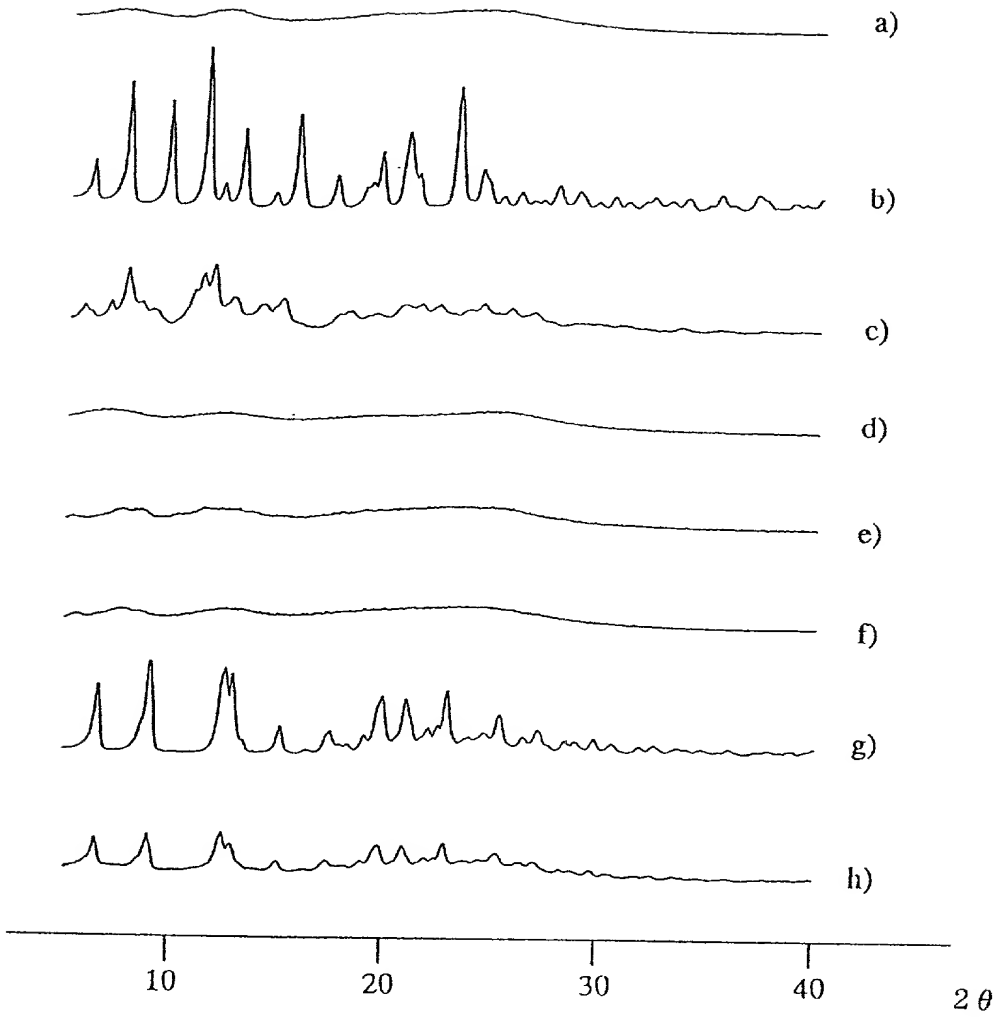
5. A process as claimed in claim 2 wherein the poor solvent is selected from the group consisting of 1-butanol, 1-butanol / acetone, 1-butanol / hexane and 1-butanol / diisopropyl ether, and the good solvent capable of dissolving the antibiotic and used in combination with the poor solvent is selected from the group consisting of water, methanol, ethanol and a mixture of two or more of them.

6. A process as claimed in claim 2 which comprises the steps of dissolving 1 part by weight of the antibiotic of formula (I) in 5 to 20 parts by weight of methanol, adding 1-butanol or a solvent mixture comprising 1-butanol / acetone, 1-butanol / hexane or 1-butanol / diisopropyl ether (in which acetone, hexane or diisopropyl ether may comprise up to 60% by volume of the solvent mixture) to the resulting solution in an amount of 1 to 20 parts by volume based on the volume of methanol, and crystallizing the antibiotic at a temperature in the range of 5 to 35°C.

ABSTRACT

Disclosed are a crystalline form of anthracycline antibiotic having specific characteristic 2θ values as measured by the X-ray diffraction method, and a process for producing the crystalline form. This process comprises the step of crystallization involving the combined use of a specific poor solvent for the antibiotic and a good solvent therefor. This crystalline form has excellent chemical and physical properties.

Fig. 1



DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

(X) Original ( ) Supplemental ( ) Substitute ( ) PCT ( ) Design

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: CRYSTALLINE ANTHRACYCLINE ANTIBIOTIC AND PROCESS FOR PRODUCING THE SAME

of which is described and claimed in:
( ) the attached specification, or
( ) the specification in the application Serial No. _____ filed _____;
and with amendments through _____ (if applicable), or
(X) the specification in International Application No. PCT/ JP98/05391, filed December 1, 1998, and as amended on _____ (if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Japan	350,157/97	December 5, 1997	Yes

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not dislcosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

ATTACHMENT B

And I hereby appoint John T. Miller, Reg. No. 21,120; Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Jeffrey Nolton, Reg. No. 25,408; Warren M. Cheek, Jr., Reg. No. 33,367; Nils E. Pedersen, Reg. No. 33,145 and Charles R. Watts, Reg. No. 33,142, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., attorneys to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from ODAJIMA & CO. as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

Send Correspondence to

WENDEROTH, LIND & PONACK, L.L.P.
2033 K Street, N.W., Suite 800
Washington, DC 20006

Direct Telephone Calls to:

WENDEROTH, LIND & PONACK, L.L.P.
Area Code (202) 721-8200

Direct Facsimile Messages to:
Area Code (202) 721-8250

Full Name of First Inventor	FAMILY NAME JOHDO	FIRST GIVEN NAME Osamu	SECOND GIVEN NAME	
Residence & Citizenship	CITY Fujisawa-shi JPX	STATE OR COUNTRY Kanagawa-ken	COUNTRY OF CITIZENSHIP Japan	
Post Office Address	ADDRESS Villa Haitsu Syonan 203, 4-27-11, Syonandai, Fujisawa-shi, KANAGAWA 252-0804 JAPAN	CITY	STATE OR COUNTRY	ZIP CODE
Full Name of Second Inventor	FAMILY NAME NAKAMURA	FIRST GIVEN NAME Kiyotomo	SECOND GIVEN NAME	
Residence & Citizenship	CITY Yatsushiro-shi JPX	STATE OR COUNTRY Kumamoto-ken	COUNTRY OF CITIZENSHIP Japan	
Post Office Address	ADDRESS Matsumura-Mansion 205, 23-4, Matsuzaki-cho, Yatsushiro-shi, KUMAMOTO 866-0884 JAPAN	CITY	STATE OR COUNTRY	ZIP CODE
Full Name of Third Inventor	FAMILY NAME YOSHIOKA	FIRST GIVEN NAME Takeo	SECOND GIVEN NAME	
Residence & Citizenship	CITY Ayase-shi JPX	STATE OR COUNTRY Kanagawa-ken	COUNTRY OF CITIZENSHIP Japan	
Post Office Address	ADDRESS 1782-10, Yoshioka, Ayase-shi, KANAGAWA 252-1124 JAPAN	CITY	STATE OR COUNTRY	ZIP CODE
Full Name of Fourth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Fifth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Sixth Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

Full Name of Seventh Inventor	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME	
Residence & Citizenship	CITY	STATE OR COUNTRY	COUNTRY OF CITIZENSHIP	
Post Office Address	ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1st Inventor Osamu JOHDO Date May 19, 2000

2nd Inventor 中村清知 Kiyotomo NAKAMURA Date May 19, 2000

3rd Inventor Takeo Yoshioka Takeo YOSHIOKA Date May 19, 2000

4th Inventor _____ Date _____

5th Inventor _____ Date _____

6th Inventor _____ Date _____

7th Inventor _____ Date _____

The above application may be more particularly identified as follows:

U.S. Application Serial No. _____ Filing Date _____

Applicant Reference Number _____ Atty Docket No. _____

Title of Invention _____